UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
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Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/230,195	12/10/99	RYBAK S	015280-28410

HM22/0216

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EXAMINER	
SORBELLO,E	
ART UNIT	**PAPER NUMBER**
1633	6

DATE MAILED: 02/16/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/230,195	RYBAK ET AL.	
	Examin r	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-35, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a cell transduction plasmid vector based on a HIV-lentiviral vector comprising a nucleic acid sequence encoding a retroviral packaging site, a splice donor (SD) , splice acceptor (SA), a retroviral Rev binding sequence, a IRES promoter sequence operably linked to the first viral inhibitor sequence wherein the inhibitor sequence is located between the SD and SA sequence, wherein the inhibitor sequence integrates into the nucleus of the cell; does not reasonably provide enablement for any transduction vector comprising the aforementioned limitations including subsequences for the viral inhibition comprising SD site subsequences, SA site subsequence and Rev subsequences, including the limitations encompassed by the claims . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to any vector comprising the limitations as set forth in claims 1-35, 41 and 42.

In view of the claims drawn to a viral inhibitor encoding an oncogene inhibitor wherein the inhibitor is an antibody binding to a ras protein or a RNAse, the specification does not teach the construction of such a vector.

In view of the claims drawn to the use of subsequences, for the viral inhibitor, DS , SA and Rev it is not clear that in the absence of teaching regarding which portion of the original viral inhibitor, DS, SA and Rev sequences that are absolutely essential to its function and need to be retained, that one of skill in the art, would be able to make and use the instant invention without undue experimentation, due to the unpredictability in the art. Therefore, It is not clear that any viral inhibitor will function to inhibit any virus, in view of the unpredictability in the art, the numerous vectors currently available and thus the breadth of the claims, and the lack of working examples.

It is known in the art of vector design and construction, that the construction of a cell transduction vector is not clear cut, as expression vectors need to be designed to direct efficient transcription and translation of cloned genes. In Molecular Cloning-A Laboratory manual by Maniatis et al. (1982), a summary of the specific teaching that is necessary for vectors constructed for a specified functions is described. (See page 433). No other vectors are described with any particularity in the instant invention, except plasmid vectors based on HIV-lentiviral vectors. Vector construction for a specified intent requires undue experimentation, due to the unpredictability in the art, as stated by Maniatis et al. with regards to selection of promoters, enhancers with specified locations for the specific transgenes inserted to encode a protein in the transduced cell. The specification did not teach each and every vector for all

transgenes directed to all types of target cells. Therefore, it would require undue experimentation to make any vector that will transduce any cell, when the specification does not teach the construction of each and every cell transduction vector.

In view of the above, it would prove an arduous task for one skilled in the art to be able to construct the vectors of the instant invention as claimed. In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

3. Claims 20 and 26 are under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transduction vectors consisting of pBAR, pBAR-ONC and pBAR-EDN, does not reasonably provide enablement for any conservative modifications of the aforementioned vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches the construction of vectors pBAR, pBAR-ONC and pBAR-EDN but does not teach each and every conservative amino acid modification as claimed.

It is well known in the art that conservative amino acid substitutions may result in altered protein phenotype and/or function. At the time of filing and subsequently

thereafter, the state of the art pertaining to conservative modifications embracing amino acid substitutions, deletions, inversions, etc. of a polypeptide is unpredictable with regard to retaining the phenotype of the polypeptide or protein. For example, Ding *et al.* teaches (see abstract) that a single conservative amino acid substitution of alanine with isoleucine in IL-10 converts the protein to a molecule with immunostimulatory activity and that "this single conservative residue alteration significantly affects ligand affinity for receptor."

It would require undue experimentation to determine the conservative amino acid substitutions in the BAR, ONC and EDN that would not alter the properties and/or phenotype of the polypeptide. The amount of experimentation required would include the trial and error determination of substitutions, deletions, inversions, etc. of single and/or multiple amino acid residues and polypeptide expression and characterization to determine whether or not the properties of the inhibitors of the aforementioned polypeptides are retained. In view of such, the invention is not enabled over the full scope as claimed.

4. Claims 29, 36, 38-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

These claims are directed to a method of transducing a cell with a nucleic acid encoding a viral inhibitor by contacting the cell with a vector comprising the limitations

of claim 1, and thus reads on *in vivo* gene therapy. Claims 29, 36 and 39 are directed to a vector modified to inhibit the replication of HIV in a cell, and to methods for inhibiting the growth of HIV, therefore reading on *in vivo* methodology. Claims 39 and 40 additionally reads on ex vivo gene therapy since the mammalian cells such as CD34+ hematopoietic cells, CD4+ cells are removed, transduced and subsequently the cells comprising the modified vector are re- introduced into the mammal.

The state of the art in *in vivo* and ex vivo gene therapy is such that both therapies are not clearly established with protocols that are used for the administration of a vector comprising a gene for the amelioration of a disease, with guaranteed results. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches that appropriate regulatory elements improve expression,

but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Crystal, R. summarized the recent experimental outcomes in ex-vivo and *in vivo* gene therapy, the strategies one must consider and the uncertainties that exist in this developing field. (See Table 1, page 406). He listed the types of vectors currently being tested for the transfer of genes for the amelioration of several diseases, in which retroviral vectors, adenoviral vectors, plasmids, liposome-plasmid complexes each with its individual advantages and drawbacks. In the case of plamids used as vectors for gene transfer he noted that the disadvantage of these is that they are inefficient, requiring thousands of plasmids presented to the target cell in order to achieve successful gene transfer. (see page 405, col. 1, para. 2). Retrovial vectors have been used to transfer therapeutic genes ex vivo in clinical trials and the proportion of genetically marked cells recovered from recipients have been observed from several weeks upto 36 months after administration. (See page 405, col. 3, para. 3). He concluded by stating that the results of human gene transfer trials have been plagued by inconsistency and that the ideal vector for these transfers is conceptually impractical because the human applications are broad and that the ideal vector is different for each application.

Therefore in view of the above the amount of direction or guidance necessary in the specification has to be very detailed in order to provide enablement. In this case, the state of the prior art does not teach one skilled in the art how to transfer a gene and induce a therapeutic response. Hence the specification requires detailed methods for

preparation of the therapeutic compositions comprising the retroviral vector with specific dosages for specific therapies as claimed by the invention. This is made clear by the MPEP 608.01(p) where it states: "If the use disclosed is of such nature that the art is unaware of successful treatments with chemically analogous compounds, a more complete statement of how to use must be supplied...".

The specification does not teach one how to introduce the vector of the invention, concentrations, site of delivery, which types of cells are to be transduced whereby the cells are then introduced ex vivo into an art accepted model in order to alleviate the symptoms of a diseased condition, except by prophetic consideration. No actual *in vivo* or *ex vivo* results have been presented. The specification teaches the administration of the vector to cultured cells and extrapolates these results to the *in vivo* and *ex vivo* situations. The pharmaceutical composition claims are not enabled for use because the language "pharmaceutical" implies that the vector of the claims provides for *in vivo* applicability particularly for treatment, but such is not enabled as are argued herein.

It is not clear that one of skill in the art could without undue experimentation use the modified vector comprising the limitations as in claim 1, for both *in vivo* and ex vivo therapy due to the paucity of appropriate teachings in the specification, unpredictability in the art, and breadth of the claims.

In view of this, it would prove an arduous task for one skilled in the art to be able to practice the claimed invention of *in vivo* and ex vivo gene therapy. Hence, since one skilled in the art cannot readily anticipate the results predicted within the subject

matter to which the claimed invention pertains, then there is a lack of predictability in the art.

In conclusion, given the nature of the invention, the state of the art, the demonstrated lack of predictability of the art, the amount of guidance set forth, the breadth of the claims, and the lack of working examples, one of skill in the art could not make and use the invention without undue experimentation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-35, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vile et al. in view of Poeschla, et al. (presented at a Colloquim entitled "Genetic Engineering of Viruses and of virus vectors" held June 9-11, 1996), published October 1996.

The claims are broadly directed to any cell transduction vector with specified limitations and a method of transducing a cell comprising contacting the cell with the vector of the invention thereby providing the cell with a viral inhibitor.

Vile et al. teach the construction of a retroviral vector comprising a splice donor site and splice acceptor,(See Fig 1A), the promoter sequence IRES to direct the translation of LTR-driven polycistronic RNA transcripts.(See sentence bridging page 16 and 17). They state that this construct is particularly attractive for expression of multiple gene products, such as cytokines and will be more effective than single expression constructs.

Vile et al. did not teach vectors for inhibiting HIV comprising an antiviral or inhibitor sequence for the treatment of such. Neither did Vile teach the inclusion of a retroviral Rev binding sequence for inclusion in a vector construct.

Poeschla, E. et al. taught murine retrovirus mediated transfer of antiviral genes into CD4+ cells or CD34+ progenitor cells ex vivo, followed by infusion of the gene altered cells into autologous or syngeneic /allogeneic recipients. They also taught lentivirus-specific biologic properties of HIVs, which underlie their pathogenetic mechanisms. (see abstract). They taught ribozymes as catalytic antisense RNAs that disrupt the target RNAs and as such function as ribonucleases or RNAse. They taught the use of two ribozymes targeting the LTR and env genes of HIV-1, each fused to an RNA decoy, the RRE(rev response) element resulted in a potent antiviral vector that effectively inhibits replication of diverse clades of HIV-1. (see page 11395, col. 2 and page 11396 col. 1 under anti-viral genes). See also Figs 1 and Fig. 2 for the general scheme for construction of packaging and vector plasmids.

As such all limitations of the claims are taught by Vile et al. in view of Poeschla et al. Therefore it would have been *prima facie* obvious at the time the invention was

made to combine the teachings of Vile et al. and Poeschla et al. resulting in plasmids based on an HIV-lentiviral vector with the subsequent addition of inhibitor sequences, to result in the instant application.

Therefore one of ordinary skill in the art would have been motivated to combine the teachings of Vile and Poeschla because Vile taught the specifics as regards vector construction and the inclusion of SD, SA, IRES and LTR sequences and Poeschla taught HIV-based lentiviral vectors. One of ordinary skill in the art would have reasonably expected success in testing the efficacy of the construct in cell lines which would not require undue experimentation.

Therefore, claims 1-35, 41 and 42 are rejected as being obvious.

Conclusion

6. Claims 1-42 are rejected.

7. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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